REMARKS

Claims 6-13 are under consideration in the current application. Claims 1-5 and 14-20 were previously withdrawn as being drawn to the non-elected invention.

By way of the present amendment, claims 7 and 8 have been cancelled and claims 6, 9, and 11-13 are amended herein.

No new matter has been added by way of these amendments.

Amendments to Claims

Claims 6, 9, and 11-13 have been amended to recite "said method comprising inhibiting the interaction of IL-1α with S100A13." Support for these amendments is found on page 12, lines 4-5 of paragraph 0071; page 12, lines 7 of paragraph 0074; page 13, lines 4-5 of paragraph 0076; page 14, lines 1-4 of paragraph 0083; page 27, paragraph 0149; page 28, lines 4-9 of paragraph 0154; pages 31-32, paragraph 0175; page 32, paragraphs 0176- paragraph 178; page 33, paragraph 0180; and page 34, paragraph 0185 in the specification.

Rejection of claim 6 pursuant to 35 U.S.C. § 102(b)

The Examiner has again rejected claim 6 as being anticipated by Applebaum et al., 1990, Free Rad. Biol. Med. 8:133-43 (hereafter referred to as "Applebaum").

It is well-established law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). Therefore, in order to anticipate these claims under 35 U.S.C. §102(b), Applebaum must describe each and every element of claim 6.

The Examiner alleges that Applebaum teaches the effect of neocuproine on cardiac injury. It is the Examiner's view that the pending claims recite using a known composition (a copper and iron chelator) and that the claimed use is a result or property of that structure. The Examiner further argues that if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. Applicants respectfully disagree with the application of this analysis to the instant claim for the following reasons.

Claim 6 is directed to a method of inhibiting neointimal formation. Applebaum discloses a method of preventing disordered electrical activity (arrhythmia) in cardiac muscle that occurs as a result of superoxide radical produced during cardiac reperfusion or exposure to hydrogen peroxide. The method of Applebaum consists of administering neocuproine to excised rat hearts that have either been exposed to hydrogen peroxide or undergone transient ligature of a coronary artery to induce temporary regional ischemia. Applebaum teaches that neocuproine, a known chelator of copper and iron, removes or alters the redox potential of redox-active metals, rendering them inactive and thereby unable to precipitate damage to cardiac muscle by superoxide radicals, ascorbate, or other free radicals. Applebaum teaches neither a method of inhibiting the interaction of IL-1α with S100A13, a method of inhibiting IL-1α release, nor a method of inhibiting neointimal formation.

In the Examiner's claim analysis, the Examiner does not afford the preamble of claim 6, "A method of inhibiting neointimal formation following vessel injury in a mammal...." any patentable weight. The Examiner further states that the phrase "thereby inhibiting said neointimal formation" in the body of the claim is a statement of intended use. The Examiner identifies the process steps in the body of the claims as administering a copper chelator in an amount sufficient to inhibit IL-1α release, wherein the IL-1α release is non-traditional IL-1α release.

The Examiner argues that in the instant case, the preamble is in accord with Jansen v. Rexall Sundown, Inc., 342 F.3d 1329, 1333-34, 68 USPQ2d 1154, 1158

(Fed. Cir. 2003) and In re Cruciferous Sprout Litigation, 301 F.3d 1343,1346-48, 64 USPQ2d 1202, 1204-05 (Fed. Cir. 2002) because, in the Examiner's view, the preamble does not limit process steps of the claim, but rather explains the purpose of the copper chelator. The Examiner further argues that because Applebaum teaches administering a copper chelator to the same population (mammals with vessel injury) the mechanism by which the inhibition occurs has no bearing on patentability.

Applicants respectfully disagree with these arguments as set forth below. When the claim is directed to a product or composition, the preamble is generally nonlimiting if the body of the claim is directed to an old composition and the preamble merely recites a property inherent in the old composition. Kropa v. Robie, 88 USPQ 478, 480 - 81 (CCPA 1951). However, if the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is "necessary to give life, meaning, and vitality" to the claim, then the claim preamble should be construed as if in the balance of the claim. Applicants respectfully argue that the preamble of claim 6 is, in fact, "necessary to give life, meaning, and vitality" to the claim and therefore must be given patentable weight.

Rowe v. Dror, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1999) discuss several criteria useful in determining whether preamble recitations are structural limitations or mere statements of purpose or use. The inquiry involves examination of the entire patent record to determine what invention the patentee intended to define and protect. First, the specification must be examined to determine whether claimed invention includes preamble recitations (In re Paulsen, 30F.3d 1475, 1479, 31 USPQ2d 1671, 1674 (Fed Cir. 1994)). Here, the instant specification explicitly teaches "a method of inhibiting neointimal formation..." as an embodiment of the present invention on page 12, line 4 of paragraph 0072; page 14, paragraph 0082; page 26, paragraph 0144; and Experimental Example 2. Second, the claims themselves should be examined to determine if the preamble recitations provide antecedent basis for terms used in the body of the claim (Gerber Garment Tech., Inc. v. Lectra Sys. Inc. 916, F.2d 683, 689, 16 USPQ2d 1436, 1441 (Fed Cir. 1990)). Here, in the instant claim, the preamble

provides antecedent basis for two essential components of the claims: (1) the method described in the body of the claim and (2) the population the method is to be practiced on. Applicants now consider each of these in turn.

The preamble of claim 6 recites a method of inhibiting neointimal formation following vessel injury in a mammal. The preamble of claim 6 is not, as the Examiner argues, a stated use, but in fact, one embodiment of the claimed invention. This is supported throughout the specification (page 12, line 4 of paragraph 0072; page 14, paragraph 0082; page 26, paragraph 0144; and Experimental Example 2 in the specification) as well as in arguments presented during prosecution which is incorporated herein (see, for example, pages 6-8 of Applicants' Amendment filed March 14, 2008).

Applicants note that the Examiner himself relies on the preamble of claim 6 to argue that Applebaum teaches administering a copper chelator to the same population as the instant claim, namely mammals with vessel injury (page 6, lines 4-5 of the pending Office Action). However, Applebaum does not teach administering a copper chelator to "mammals having a vessel injury." The population that Applebaum is treating is a population experiencing arrhythmia, an uncoordinated and chaotic electrical activity in the heart's conduction system that prevents the heart from contracting and relaxing as a whole. This disorder of electrical conduction in heart muscle is caused by the presence or accumulation of superoxide radicals in cardiac muscle tissue. The injury is measured as a reduction in cardiac function because the electrical conduction in the heart muscle is too disordered to sustain efficient muscle contraction. Even when the arrhythmia is caused by ischemia produced by transient ligature of a coronary artery, the vessel itself is not damaged; only the cardiac muscle deprived of oxygen is damaged. Accordingly, Applebaum does not teach treating a population with vessel injury. Therefore, Applebaum does not teach administering a copper chelator to the same population as "mammals having a vessel injury" and certainly does not teach a method of inhibiting neointimal formation following vessel injury, either explicitly or implicitly.

In further support of Applicants' argument, Applicants note that the Examiner in the present Office Action actually relies on the preamble of claim 6 to

distinguish claim 6 from claims 7 and 9. The Examiner simply cannot have it both ways. The preamble of claim 6 breathes life and breath into the claim, even according to the Examiner, and therefore lends patentable weight to the claim, thereby distinguishing the claim over Applebaum.

While not in agreement with the Examiner's arguments, but solely in an effort to expedite prosecution, Applicants amend claim 6 herein to recite "... said method comprising inhibiting the interaction of IL-1α with S100A13." Applebaum does not teach inhibiting the interaction of IL-1α with S100A13, therefore Applebaum cannot anticipate the claimed invention. In view of the arguments and amendments made herein, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of claims 6, 9, and 11-13 pursuant to 35 U.S.C. § 102(b)

Claims 6, 9, and 11-13 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Brewer et al., (WO 200013712; hereafter referred to as "Brewer").

The Examiner alleges that the present claims are anticipated because they essentially recite using an old structure or composition (a copper chelator) and that the result is a property of that structure or composition. The Examiner further argues that Brewer teaches a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis by administering the copper chelator tetraiomolybdate (TTM). The Examiner therefore alleges that Brewer teaches administering TTM to the same population and for the same purpose claimed by the Applicants in the instant invention (page 7, paragraph 2).

This is simply incorrect both factually and in terms of interpreting Brewer as an anticipating reference of the present invention. Brewer is directed to a method of treating all forms of solid tumors having a vascular component by administering a composition comprising a copper chelator to induce systemic copper deficiency. Brewer contemplates applying the method to other diseases or aberrant vascularization including preferred embodiments where the disease is arthritis, cancer, and wet type macular degeneration. Brewer further contemplates other diseases characterized by aberrant

angiogenesis (page 53, lines 20-29) or retinal neovascularization (page 56, lines 8-19). Brewer states that "it is believed" that angiogenesis is "involved" in rheumatoid arthritis (page 56, lines 20-21), and "may play a role in osteoarthritis" (page 56, lines 29-30). Finally, Brewer contemplates that "chronic inflammation may also involved pathological angiogenesis." No where does Brewer contemplate inhibiting neointimal formation, macrophage infiltration, cell proliferation, secretion of extracellular matrix or adventitial angiogenesis related to vessel wall injury, the as-claimed embodiments of the instant invention. Nor does Brewer contemplate inhibiting IL-1α release from a cell, or the inhibition of IL-1α with S100A13 interaction, additional limitations of the instant claims.

Brewer suggests that both normal and uncontrolled angiogenesis use similar pathways (page 41, lines 7-16). By extension, Brewer suggests that free copper would play a similar role in each of these processes, but neither Brewer nor the relevant art support this assertion. As it is well known in the art, and which Brewer himself states, angiogenesis is a tightly regulated physiological phenomenon that occurs only rarely and under specific instances of wound healing, embryonic and fetal development, and endometrial and placental development. This is contrasted with the persistent, unregulated angiogenesis that occurs during tumor growth and metastasis. In fact, these can be considered two very different processes and the resulting capillaries and blood vessels do not have a normal appearance.

Brewer outlines the well accepted process of angiogenesis as follows (page 41, lines 7-16): angiogenesis begins with the erosion of the basement membrane by enzymes released by endothelial cells and leukocytes. The endothelial cells which line the lumen of blood vessels then protrude through the basement membrane. Angiogenic stimulants induce endothelial cell migration through the eroded basement membrane. The migrating cells then sprout off the parent blood vessel, where the endothelial cells undergo mitosis and proliferation. The endothelial sprouts merge with each other to form capillary loops thereby creating a new vessel.

In contrast, a blood vessel responds to injury with a very different sequence of events (reviewed in Morton et al., 2005, Cardiovasc. Res. 68:493-501). This

is particularly relevant to restenosis, a major limitation of balloon angioplasty. The cell biology of vessel response to injury, as characterized by restenosis, has been extensively studied and is well known in the art. The injured blood vessel responds to injury in a characteristic manner, that is, by neointimal formation. The neointima is formed from recruited vascular smooth muscle cells that proliferate, migrate, and secrete an extracellular matrix that narrows the vessel lumen (Virmani, 1999, Curr. Opin. Lipidol. 10:499-506). The stereotypical response to vessel injury follows a classic inflammatory paradigm. Injury causes an up-regulation of adhesion molecules in the vessel wall which in conjunction with adherent thrombus direct leukocyte accumulation. Inseparable from white cell recruitment is the synthesis and release of inflammatory signaling molecules that transduce the inflammatory signal (cytokines) and direct white cell migration (chemokines). Amongst the inflammatory cytokines, IL-1α is central to the initiation of many inflammatory signals. Consequently, the novelty of the instant invention is specifically directed to a method of inhibiting a blood vessel's stereotypical response to injury by blocking IL-1α release.

Indeed, the assumption that blood vessel cells in healthy tissues and those associated with tumors are similar has been unequivocally demonstrated to be incorrect. Simply put, tumor blood vessels are not normal vessels. In fact, tumor-specific blood vessel cells are atypically stem cell-like and have the potential to differentiate into cartilage- or bone-like tissues. These results suggest that tumor blood vessel endothelial cells possess a stem/progenitor cell property that distinguishes them from endothelial cells throughout the normal vasculature and undergo atypical differentiation (Dudley et al., 2008, Cancer Cell 14:201-211).

It will be readily appreciated by a skilled artisan that angiogenesis in malignant tissue and a blood vessel's response to injury are very different physiological processes occurring with very different cell populations. Accordingly, a method for inhibiting angiogenesis in malignant tissue cannot be considered predictive of a method for inhibiting neointimal formation in response to vessel injury. Nor could a skilled artisan predict with any expectation of success that a composition that is effective in

inhibiting angiogenesis in malignant tissue would have a similar effect in inhibiting neointimal formation in a blood vessel responding to injury.

Further, Brewer provides data solely for the effect of a copper chelator on tumor growth. Nowhere does Brewer present any data that supports his suggestion that systemic copper reduction inhibits angiogenesis. Brewer simply speculates that free copper may have a role in angiogenesis based on neovascularization studies performed on rabbit cornea (page 2, lines 3-13). The fact that tumors in mice administered a copper chelator do not grow as rapidly as those in mice left untreated in no way supports the idea that copper is an essential component for angiogenesis in malignant tissues. That is pure conjecture on the part of Brewer.

Thus, Brewer merely speculates that free copper plays a role in tumor angiogenesis, but provides no evidence that this is the case. Nor is there any substantive evidence anywhere in the art that angiogenesis in malignant tissues is a comparable process to a blood vessel's response to injury. For these reasons, a skilled artisan following the teachings of Brewer would have no reasonable expectation that free copper could inhibit IL-1α release from a cell, and thereby block the inflammatory cascade of cellular events that lead to neointimal formation in response to blood vessel injury. Thus Brewer cannot anticipate the present invention. Applicants respectfully submit that the rejection is improper and request its withdrawal.

Rejection of claims 6-13 pursuant to 35 U.S.C. § 103(a)

The Examiner has rejected claims 6-13 under 35 U.S.C. §103(a) as being obvious over Brewer et al., (WO 200013712) and Wempe et al., 1997, Arterioscler. Thromb. Vasc. Biol. 17:2471-8 (hereafter referred to as "Wempe") as evidenced by Dayer et al., 1993, Ann. Rev. Respir. Dis. 148:S70-4 and Issekutz, 1995, J. Immunol. 154:6533-6540. To the extent that this rejection applies to claims 7 and 8, this rejection is rendered moot in view of the cancellation of these claims herein. Applications' response to this rejection therefore applies solely to claims 6 and 9-13.

The test which must be met for a reference or a combination of references to establish obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part, the proper test for obviousness:

> Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103... [T]he four factual inquires enunciated therein as a background for determining obviousness are as follows:
> (A) Determining the scope and contents of the prior art;
> (B) Ascertaining the differences between the prior art and the claims in issue;
> (C) Resolving the level of ordinary skill in the pertinent art; and
> (D) Evaluating evidence of secondary considerations. MPEP § 2141.

Additionally, MPEP § 2143.01 provides: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)." (emphasis added).

Further, it is well-established law that each prior art reference must be evaluated in its entirety, and all the prior art must be evaluated as a whole. *Hughes Aircraft Co. v. United States*, 15 Cl. Ct. 267, 272 (Ct. Cl. 1988), citing *Panduit Corp. v. Dennison Manufacturing Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985), *vacated*, 475 U.S. 809 (1986), *on remand*, 810 F.2d 1561 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987).

The deficiencies of Brewer have been discussed in detail above and are not repeated here. Briefly, Brewer cannot render the instant invention obvious because a method of using a copper chelator to treat neovascularization and aberrant angiogenesis of tumors and malignant tissues, as taught by Brewer, provides no teaching that would lead a skilled artisan to arrive at a method of inhibiting IL-1α release from a cell to prevent neointimal formation, (claim 6), cell proliferation associated with arterial wall injury (claims 9 and 10); secretion of extracellular matrix following arterial injury (claim 11); neointimal thickening associated with arterial wall injury (claim 12), or adventitial angiogenesis associated with arterial wall injury (claim 13).

Wempe discloses preferential adhesion of monocytic cells to migrating endothelial cells after balloon denudation injury. Wempe also teaches that mRNA expression for the chemokine MCP-1 is increased in aorta endothelial cells after balloon denudation injury. Wempe further discloses that endothelial cells stimulated with basic fibroblast growth factor (bFGF) have greater expression of MCP-1 than unstimulated cells, leading Wempe to suggest that bFGF may act as an autocrine regulator of endothelial cell activity and inflammatory cell trafficking.

Wempe does not teach a role for IL-1α in monocyte adhesion. Further, Wempe does not teach a method of inhibiting IL-1α release from a cell, the use of a copper chelator to inhibit IL-1α release from a cell, or a method to prevent macrophage infiltration (claims 7 and 8) by inhibiting IL-1α release from a cell. Wempe would not direct a skilled artisan to the present invention because Wempe teaches the importance of bFGF in MCP-1 expression and consequently suggests that bFGF is a mediator of inflammatory cell trafficking following balloon denudation injury. Because the mechanism of regulating MCP-1 expression by bFGF stimulation of endothelial cells as taught by Wempe neither predicts nor suggests the effect of IL-1α on macrophage infiltration or a method of inhibiting IL-1α release from a cell, Wempe would not lead a skilled artisan to arrive at the present invention comprising a method of inhibiting IL-1α release from a cell or the use of a copper chelator to inhibit IL-1α release from a cell to prevent macrophage infiltration. Nor does the mechanism elucidated by Wempe suggest a method to prevent cell proliferation associated with arterial injury (claims 9 and 10), secretion of extracellular matrix following arterial injury (claim 11) or neointimal thickening (claim 12) that encompasses inhibiting IL-1α release from a cell. Accordingly, the present invention cannot be obvious over Wempe, either alone or in combination with Brewer.

The Examiner alleges that Dayer provides evidence that cell-associated IL-1α plays a crucial role in the process of cell-cell interaction between monocytes and fibroblasts and that this interaction may be inhibited by IL-1α inhibitors. The Examiner also alleges that Issekutz provides evidence that IL-1α plays a crucial role in the process

of cell-cell interaction between monocytes and endothelial cells. However, none of Dayer or Issekutz disclose method of inhibiting IL-1α release from a cell following blood vessel injury in order to inhibit neointimal formation (claim 6); cell proliferation associated with arterial wall injury (claims 9 and 10); secretion of extracellular matrix following arterial injury (claim 11); neointimal thickening associated with arterial wall injury (claim 12), or adventitial angiogenesis associated with arterial wall injury (claim 13). Accordinly, neither Dayer nor Issekutz can redress the deficiencies of Brewer and Wempre, either alone or in combination.

Applicants respectfully submit that the rejection of claims 6 and 9-13 under 35 U.S.C. § 103(a) is improper and does not apply. Applicants respectfully request reconsideration and withdrawal of the rejection.

Summary

Applicants respectfully submit that the pending claims, including the amended claims, are fully supported in the specification as filed, and that no new matter has been added by way of the present Amendment and Response.

Favorable examination and allowance of the claims is hereby requested.

Respectfully submitted,
THOMAS MACIAG, et al.

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Date

QUANG D. NGUYEN, Ph.D.
Registration No. 52,066
DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
Tel: (215) 988.2720
Fax: (215) 988.2757
Agent for Applicant